

# Left Atrial Appendage Obliteration

## Mechanisms of Healing and Intracardiac Integration

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**Objectives** The objectives of this study were: 1) to delineate the temporal course of histopathologic healing as the left atrial appendage (LAA) is obliterated by a mechanical device; and 2) to compare this process with other intravascular and intracardiac implanted technologies.

**Background** Intracardiac device healing is incompletely understood. We thus studied the histopathology of device-based LAA obliteration.

**Methods** Nine dog hearts were examined over time after LAA device placement and results were compared with human hearts with prior LAA obliteration using the same device.

**Results** At 3 days in dogs, atrial surfaces were covered by fibrin, which sealed gaps between the LA wall and the device and filled the LA appendage cavity. At 45 days, endothelial cells covered the endocardial surface with underlying smooth muscle cells that sealed the device-LA interface. Regions with prior thrombus were replaced by endocardium surrounding the device membrane. Disorganized thrombus remained in the LAA body and at the periphery near the appendage walls. Mild inflammation was observed as thrombus resorbed. By 90 days, a complete endocardial lining covered the former LAA ostium. Organizing thrombus had become connective tissue, with no residual inflammation. The human necropsy hearts had similar findings. In these 4 hearts (139, 200, 480, and 852 days after implant), the ostial fabric membrane was covered with endocardium. The appendage surface contained organizing thrombus with minimal inflammation. Organizing fibrous tissue was inside the LAA cavity, prominent near the atrial wall. The LAA interior contained organizing thrombus.

**Conclusions** This intracardiac device integration study delineated healing stages of early thrombus deposition, thrombus organization, inflammation and granulation tissue, final healing by connective tissue, and endocardialization without inflammation. These observations may yield insight into cellular healing processes in other cardiac devices. (J Am Coll Cardiol Intv 2010;3:870–7) © 2010 by the American College of Cardiology Foundation

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The histopathologic healing and integration of implantable intracardiac devices is incompletely characterized (1,2). Scattered reports document the healing of heart valves (3–6) and atrial septal occluders (7–9) but do not put these processes into a larger context, especially because such processes may be similar to stent healing in coronary arteries (10–13). Because many new intracardiac devices for structural heart disease are undergoing clinical evaluation (e.g., atrial septal defect, patent foramen ovale closure), a comparative description of device healing could provide a useful comparison. This study thus examined the healing histopathology of a device designed to obliterate the left atrial appendage (LAA) using a fabric membrane covering multiple metal support struts (Fig. 1). The study specifically sought to evaluate the device-tissue interface of the Watchman (Atritech, Inc., Plymouth, Minnesota) after percutaneous, permanent implant into the body of the LAA, with especial interest dealing with both safety and efficacy (14–18).

## Methods

The study was approved by the Institutional Animal Care and Use Committee of the University of Minnesota and conformed to the position of the American Heart Association on use of animals in research.

Watchman LAA obliteration devices were implanted in the LAA of 9 dogs via surgical open visualization using thoracotomy and a venous transseptal method. Femoral venous access was obtained via intravascular sheath. Under fluoroscopic visualization, devices were placed in the LAA via transseptal approach. A left fourth- or fifth-intercostal space thoracotomy was also performed to directly observe the implant. Post-operatively, a thoracotomy tube was placed and connected to a water-sealed chest drain. The thoracotomy tube was removed when the dog was stable and spontaneously breathing.

Cephalexin 30 mg/kg was administered intramuscularly within 24 h of the procedure and continued twice daily for 7 days post-operatively. Gentamicin 3 mg/kg was given intravenously within 24 h of surgery and on the day of surgery. Aspirin 325 mg was given orally twice daily on the day of surgery and then once daily for the duration of the study. One day before the procedure, warfarin 6 mg/day was given orally and continued until euthanasia. This warfarin regimen was implemented in dogs to mimic a program expected in the human clinical trials that were planned to follow the pre-clinical dog studies, including the chronic time points.

The animals were euthanized in 3 groups at different time points: 3 animals at 3 days following implant (Group I), 3 animals at 45 days (Group II), and 3 animals at 90 days (Group III). Euthanasia was accomplished immediately after final fluoroscopic imaging. Animals were heparinized

and death was induced by lethal intravenous doses of a commercial solution (Beuthanasia, Schering-Plough, Kenilworth, New Jersey). After euthanasia, pathologic and histopathologic analysis was performed via standard methods.

At necropsy, the kidneys, livers, spleens, and lungs were inspected for evidence of infarction or other pathology. Following this, the hearts, lungs, livers, spleens, and the kidneys were immersion-fixed in 10% neutral buffered formalin for 48 h. Devices were evaluated for positioning, completeness of seal, penetration of struts, atrial appendage distention, and appearance of the atrial prosthetic device surface. The LAA, device, and the adjacent atrial wall were dehydrated in a graded series of ethanol and embedded in methyl methacrylate plastic. After polymerization of the plastic, 3 to 4 equidistant longitudinal sections approximately 0.5 cm in thickness were sawed through the device and the atrial appendage and wall. The sections were ground to a thickness of 40 to 50  $\mu$ m using Exakt Linear Grinding (Exakt Medical Instruments, Oklahoma City, Oklahoma) technology, polished, and stained with toluidine blue and basic fuchsin stains. All sections were examined by light microscopy for inflammation, thrombus, neointimal formation, endothelialization, LAA obliteration, and device sealing of the LAA. Atrial appendage histopathology was examined with special attention to the atrial surface and to evaluate the tissue response surrounding and within the device.

Four human hearts with devices were also available for study. In each case, the patients died of causes unrelated to the device or procedure. In these patients, the anticoagulation regime was warfarin after implant that was then discontinued on day 45. Hearts were obtained from patients dying at 39, 200, 480, and 852 days after implantation. All hearts were examined grossly before embedding in methyl methacrylate plastic.

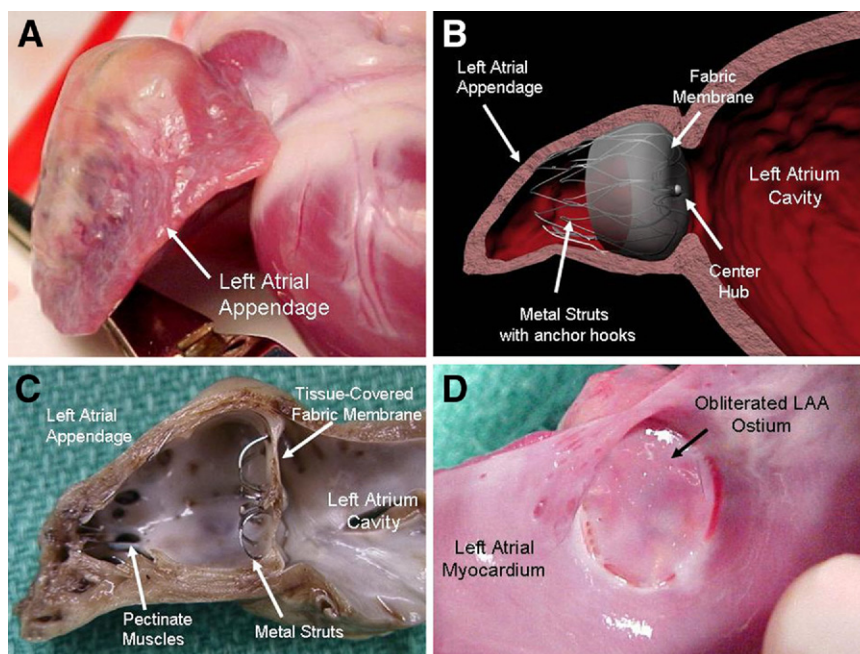
## Abbreviations and Acronyms

LAA = left atrial appendage

## Results

All dog implants were performed successfully without complication. Devices were appropriately placed within the LAA, beyond the appendage/atrial ostium. There was no gross or microscopic evidence of infarction in any of the organs including the heart in all animals, suggesting no significant embolization to these organs. There was no evidence of trauma to the underlying left circumflex coronary artery in all 9 hearts.

**Dog Group I: 3 days.** One early death occurred in Group I on the day the animal was to be euthanized. Autopsy evaluation revealed an intrathoracic hemorrhage that originated from the area of the left internal mammary artery near the thoracotomy site. There was no hemopericardium, and



**Figure 1. Composite Images of the LAA and Obliteration**

(A) Post-mortem dog heart (no device implanted), showing the exterior view of the left atrial appendage (LAA). (B) Diagrammatic view of the Watchman LAA obliteration method. Metal struts with anchoring hooks secure the device within the body of the appendage cavity. A fabric membrane filter covers the atrial surface of the device, preventing thrombi from escaping into the left atrial chamber. A center hub is used to connect the device to the catheter delivery system. (C) Dog autopsy specimen 28 days after Watchman implant showing a cross-sectional cutaway view of the Watchman device. The fabric membrane is covered with a fine layer of endocardium, and the metal struts are shown holding the device in place. Pectinate muscles internal to the LAA cavity are labeled. (D) Dog autopsy specimen showing a view of the former LAA ostium, now completely obliterated by the endocardium-covered fabric membrane. This view is from the left atrial cavity, where it is clear that thrombi potentially residing the left atrial appendage body could no longer escape into the left atrium and systemic circulation.

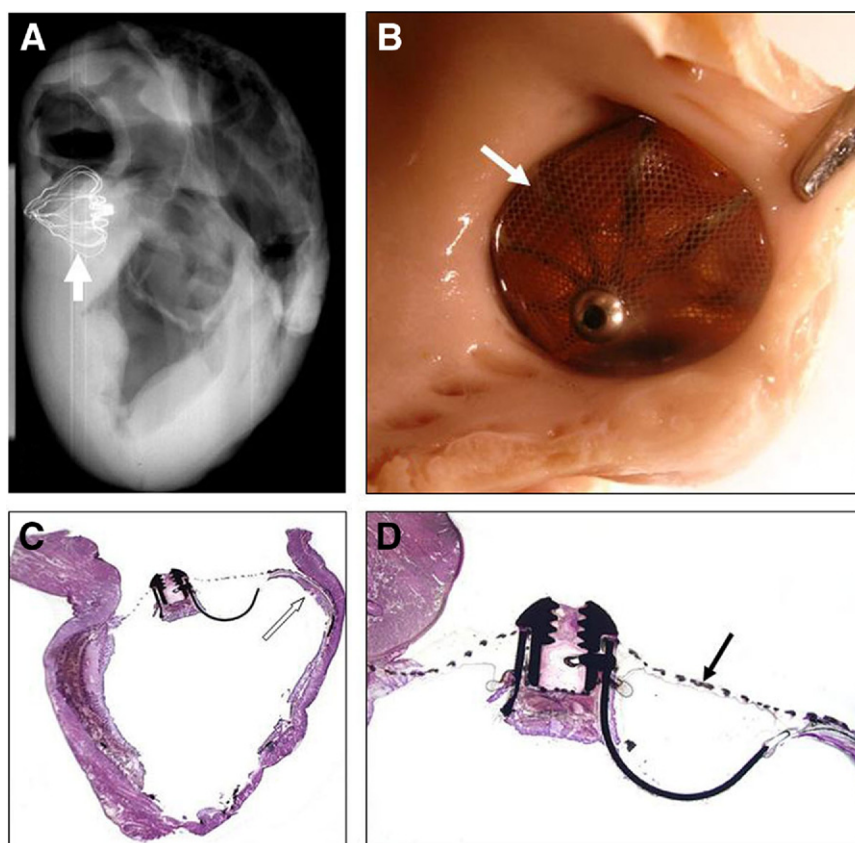
a subcutaneous hematoma in the left thorax and abdomen suggested that hemorrhage did not occur from the heart. This was thus considered a procedural- rather than a device-related death.

In all cases, before removal of the heart, the pericardium could be easily separated from the heart surface, as only a mild pericarditis was evident. This mild pericarditis was focal only. The late groups showed no apparent effects of chronic pericarditis.

All devices in Group I could be easily removed from the LAA. Consistent accumulation of organizing thrombus covered the prosthetic device atrial surface and was of variable thickness (Fig. 2). A neutrophilic infiltrate was frequently observed, with the organizing thrombus also showing some macrophages. The myocardium at the junction of the implant showed focal necrosis likely due to the struts and fabric pressure creating compression atrophy. Perforation of 2 wires through the epicardium was seen in 1 implant, but without apparent consequence. The wires were not broken. The inner lumen of the device was filled with acute thrombus in only 1 device, whereas the other 2 showed partial filling.

**Dog Group II: 45 days.** The fabric membrane of the prosthetic device at the LAA opening had an organized neoendocardial surface. The glistening white pannus on the atrial surface of the device was thin, but was substantially thicker beneath the membrane, on the LAA side. It also showed an extension of the ingrowth into the LA wall surface (Figs. 3 and 4). A moderate granulomatous inflammation occurred near the woven material. Histopathologic examination showed it was granulation tissue lined by a thin layer of endothelial-like cells. Endocardial ingrowth completely covered all exposed surfaces and was continuous with the LA surface, which resulted in effectively sealing the device-LA interface. Prior fibrin deposition had been replaced by an endocardium, which consisted of smooth muscle cells in a proteoglycan-collagenous matrix that surrounded the metal and fabric elements (Fig. 3).

**Dog Group III: 90 days.** In Group III, fibrous tissue pannus encapsulated the woven fabric on the prosthetic atrial wall. The fibroblastic response was accompanied by none or a mild inflammatory response with occasional chronic granulomatous reaction. The tissue had a monolayer of



**Figure 2. Dog Heart 72 H After Device Implantation**

(A) Postmortem in vitro X-ray showing position of the left atrial appendage obliteration device (arrow). (B) Gross photograph showing that the device membrane (arrow) is coated with a thin layer of fibrin. (C,D) Methyl methacrylate-embedded sections showing thin fibrin coating on the membrane (black arrow) and fibrinous sealing of the membrane to the left atrial wall (white arrow).

endothelial-like cells covering a healthy neoendocardium, which consisted of smooth muscle cells in a collagenous matrix. The woven fabric and metallic center of the device were visible due to formation of a thin tissue covering at these sites.

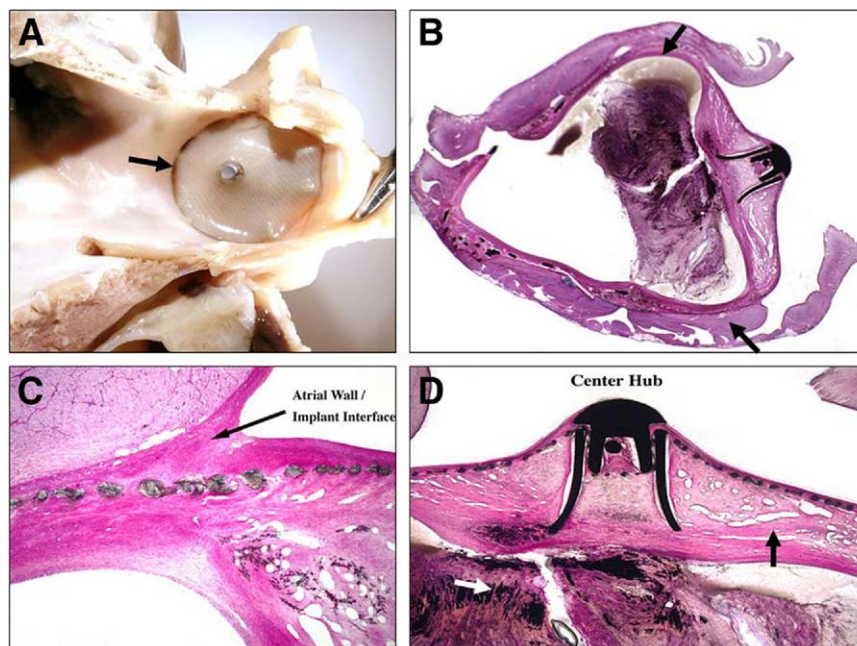
Widely organized chronic thrombus within the atrial appendage device showed significant angiogenesis in Groups II and III. Two animals (1 each from Groups II and III) had an empty lumen in the distal part of the LAA device, and the lumen was lined by a collagenous capsule. In 3 animals, a communication occurred between the pectinate atrial muscle and the distal part of the appendage. This communication was small, and the body of the appendage was filled with healing fibrotic tissue.

The temporal changes in the 90-day dog group in comparison to the 45-day group are principally those of continued healing, with continued resorption of the thrombus mass trapped in the obliterated appendage within the device, and continued replacement with collagen and pannus.

At all time points, search for emboli via pathology showed no evidence of acute or chronic emboli to the coronary arteries or brain.

**Human hearts.** Four human hearts with prior device implant were available for review. Causes of death were unrelated to the device. Gross and histopathologic findings in these hearts were similar to those in Group III of the dogs. In these hearts (139, 200, 480, and 852 days following implant), the fabric membrane showed varying coverage with organized endocardium (Figs. 4 and 5). Two devices showed an early organizing, thin laminar fibrin thrombus covering most of each device's atrial surface. Neither of the exterior thrombi had substantive mass, and neither looked brittle or fragile. Organized neoendocardial growth sealed the interfaces of each device and native appendage wall. The third and fourth devices showed an organizing endocardial growth covering approximately 85% to 90% of each device's surface, which was thicker near the appendage wall interface. The overgrowth contained well-organized collagen that was continuous with the native appendage wall. An





**Figure 3. Dog Heart, 45 Days After Device Implantation**

(A) A glistening white pannus covers the left atrial surface of the device (**arrow**). (B) The neoendocardial covering is continuous from the left atrial wall to the device (**arrows**), effectively locking the device in place and preventing exit of any residual thrombus from the interior of the obliterated left atrial appendage chamber. (C) The interface between the device membrane and the left atrial wall is completely sealed by fibrous tissue (**arrow**). (D) The neoendocardium was thin on the atrial chamber surface but was substantially thicker beneath the membrane (**black arrow**). Dense, organized fibrin is being resorbed from the interior of the left atrial appendage device. The **white arrow** points to, and is within, a large region of organizing thrombus. This thrombus is coagulation of the whole blood trapped within the appendage after device placement.

endothelial cell monolayer lined the neoendocardium near the LAA/luminal interface though there was no appreciable endothelial coverage over the center of each device. On each device's undersurface (appendage cavity side), an organizing thrombus covered the membrane, without significant inflammation at the strut or fabric site. Organizing fibrous tissue was seen inside the LAA in varying degrees, prominent at and near the atrial wall. Each device's interior contained red blood cells and organizing fibrin thrombus, similar to that observed in the pre-clinical studies. The inner tip of the appendage of the 852-day implant showed blood filled trabecular spaces possibly fed by collateral circulation from the appendage wall.

The variability in organized neoendocardial coverage over the devices was possibly due to placement within the appendage. Healing reactions were similar between animals and humans, but animal healing was faster.

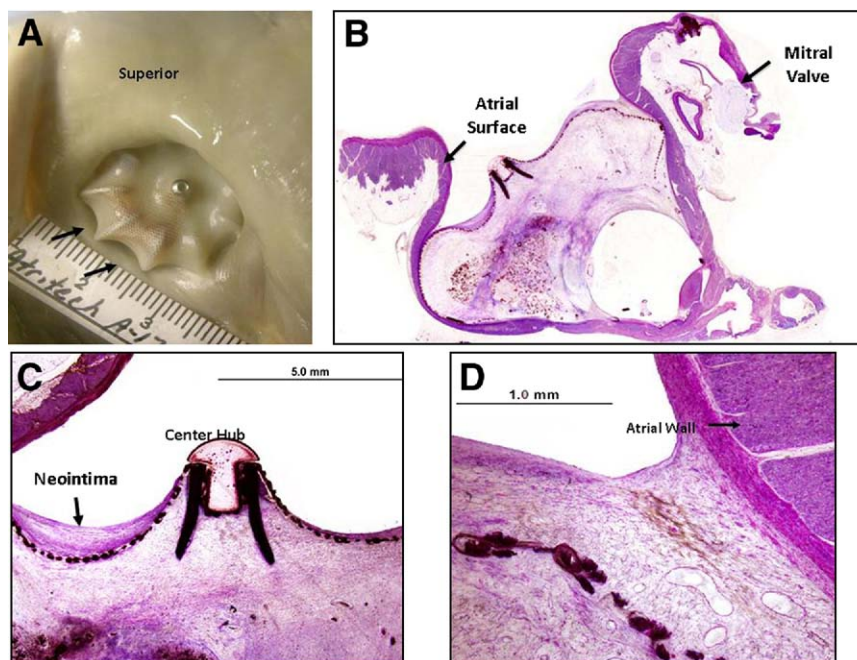
## Discussion

This study describes device healing after LAA obliteration over time from a histopathologic and macroscopic perspective. Results in dogs and patients were similar to an earlier

device that did not complete large-scale development (Per-cutaneous Left Atrial Appendage Transcatheter Occlusions [PLAATO] device, ev3, Plymouth, Minnesota) (19,20). The Watchman LAA device implant caused mild distention and atrial appendage expansion, with mild LA epicarditis and no significant pericarditis. Early sealing was partial to complete, and the interior of the LAA subsequently filled with thrombus in most cases that eventually organized. The angiogenesis found within the organizing appendage thrombus and its communication with pectinate appendage muscle in the distal part of the appendage likely have no clinical findings, because this anatomic occurrence is within the obliterated portion of the appendage body.

The LA surface of the device became covered with a new endocardium (observed in all 4 patients), including 1 at the earliest human time point of 139 days. This neoendocardium occurred over the prosthetic atrial device surface and was probably the result of organization of a fibrin-rich thin layer of thrombus, through granulation tissue with eventual replacement by smooth muscle cells in a proteoglycan-collagen matrix and endothelialization.

The canine species has substantial variability in LAA lobular structure, as do humans. This likely influences the



**Figure 4. Human Heart 200 Days After Implantation**

(A) Opened left atrium showing the device seated within the appendage orifice. There are small linear gaps between the concave surface of the device fabric and the edge of the appendage ostium margin (arrows), though the appendage cavity behind the covered membrane was healing with endocardium so no thrombi could form nor exit this appendage. (B) Sagittal section through the center of the appendage and device. The section shows tight apposition of the device to the appendage wall and sealing of the device-appendage wall interface. Inside the device, the **reddish-pink** areas indicate fibrous organization. Toluidine blue and basic fuchsin stain. (C) Close-up view through the center of the device showing neointimal coverage over the surface. Toluidine blue and basic fuchsin stain, 1.25 $\times$ . (D) Close-up view of the device surface showing effective sealing of the atrial wall-device interface (arrow). Brown areas represent hemosiderin resulting from red cell breakdown. Toluidine blue and basic fuchsin stain, 4 $\times$ .

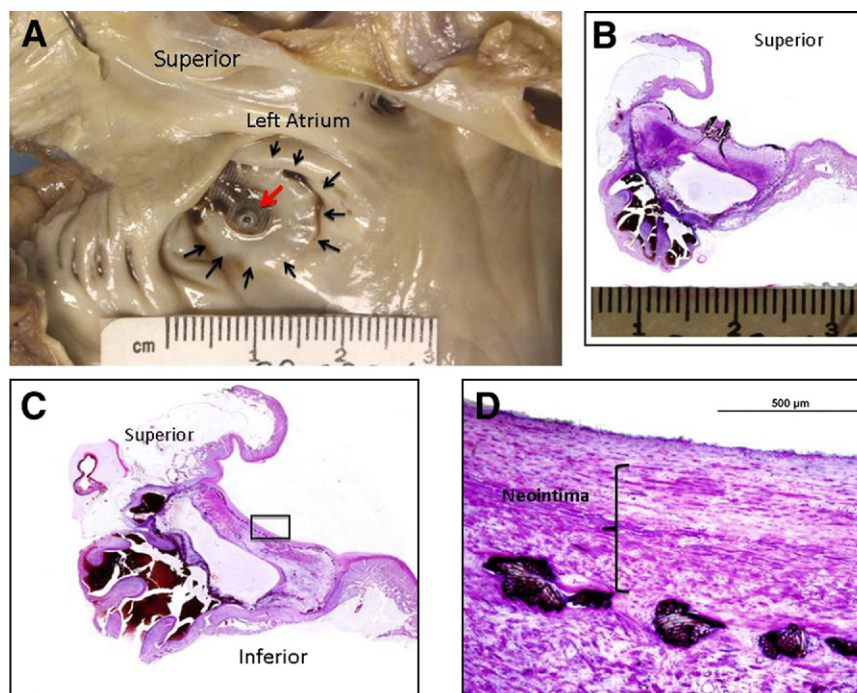
healing in only a minor way, because the majority of healing occurs at the LAA ostium rather than in the recesses of the appendage body. The continuity of histopathologic healing with LAA obliteration and with other intracardiac devices such as valves is apparent. For example, healing after surgical injury to mitral valves was studied in sheep by Tamura et al. (4). An in vitro study (5) showed that multilayered endocardial cells cover wounded regions early, within 4 to 6 days. Endocardial layers consist of endothelium and coalesced myofibroblasts growing within the granulation tissue that forms after thrombus deposition. van den Brand et al. (21) showed young scar tissue occurring at injury sites of the aortic valve following valvuloplasty as late as 24 months, also accompanied by mature fibrous tissue.

Interestingly, the Watchman LAA obliteration device heals comparably in both dogs and humans through a process similar to intracoronary stents: a fibrin-rich thrombus that organizes by an inflammatory granulation tissue reaction, followed by pannus formation consisting of smooth muscle cells in a proteoglycan-collagenous matrix and surface endothelialization with continued thrombus resorption (10,13,22,23).

Safety and efficacy of the LAA obliteration as related to histopathology entails several considerations. The device process appeared safe in that no macroscopic thrombus of any sort (loose or attached) was found on the fabric membrane at the observed time points. Fibrin on the membrane was thin and laminar, covering and becoming part of the membrane. Even though the human pathology data showed that 85% to 90% of the surface was covered by endothelium, this likely has little influence as evidenced by the PROTECT-AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) clinical trial that showed 32% fewer clinical events in the device-treated group versus the warfarin-only treated group (24).

Efficacy can be estimated by observing the device sealing off the appendage ostium. The device edges showed tissue continuity with the appendage ostium in all cases, leaving neither spaces nor other mechanism residual appendage body contents to exit the appendage cavity. The device similarly integrated into the wall, so that it could not itself embolize.

Healing of blood-containing organs and blood-contacting surfaces is a fundamental biologic process because reliable



**Figure 5. Human Heart 852 Days After Implantation**

(A) Atrial view of a human heart, showing the left atrial appendage ostium obliterated by the implanted device, 852 days after implantation. The center of the device is indicated by the red arrow. Black arrows show the lip of the former ostium, now obliterated. Residual post-mortem blood is seen at the device-atrial interface. (B) Sagittal section through the center of the appendage and device. The section showed tight apposition of the device to the appendage wall and sealing of the device-appendage wall interface (arrows). Inside of the device, the reddish-pink areas indicated early fibrous organization. (C) Low-power view for orientation of high-power view shown in (D). This is the left atrial surface. (D) Close-up view of the left atrial device surface showing an organized endocardial layer covering the surface near the center of the device. Toluidine blue and basic fuchsin stain.

and rapid cellular function is imperative to species survival. This study confirmed continuity of such key healing processes across species (humans and dogs), devices (cardiac valves, LAA occluders, and vascular stents), and anatomic location (intracardiac and intra-arterial), suggesting a universal and fundamental set of cellular events. For example, Hara et al. (25) showed a very similar result for patent foramen ovale closure healing with a radiofrequency-based welding to shut the patent foramen ovale membranes. Two other papers (9,26) describe intimal tissue formation in atrial septal defect occlusion devices, showing progressive diminution of macrophages, and fibroblast growth with maturation over a 10-week period.

These healing events begin with fibrin-thrombus deposition (initially unorganized, later dense and organized), followed by controlled inflammation consisting of macrophages and lymphocytes resorbing the thrombus. Smooth muscle cell infiltration and fibrous tissue generation then lead to endothelial coverage resembling the endocardium that develops a final, biocompatible blood-contacting interface. These events, when understood, may prove useful for designing new technologies or enhancing

biocompatibility of older devices for intracardiac and intravascular application.

**Study limitations.** There are several important limitations to this study. The dog studies showed faster healing than the patients did, though the histopathology was comparable albeit on a different time scale.

The duration of warfarin therapy was chronic in the dogs, though shorter in the patients. The impact is uncertain, though there was congruence between human and animal histopathology regarding thrombus on the device membrane. The implications of healing in the animal study with respect to warfarin therapy in the dogs are principally that of timing, as has been true with coronary stents. However, this may be beneficial, with animal models showing the healing on a shorter time scale. The human healing time course appears to be compressed in the animal model.

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**Key Words:** atrial fibrillation ■ embolic stroke ■ left atrial appendage.